REMARKS

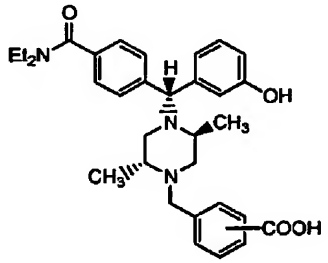
Amendment of Claims 8, 14 and 31

Claims 8, 14 and 31 have been amended. Support for these amendments can be found throughout the specification and claims as originally filed at, for example, page 2, lines 11-13, page 4, lines 5-8, page 8, line 18 through page 9, line 7, page 28, line 7 through page 37, line 19, and original claims 1.

Correction of Office Action Detailed Action

In response to the March 28, 2006 Office Action, Applicants respectfully submit that Group II, claims 8, 14, 20-28 and 31-40, drawn to a method of using the compositions of the present invention, was elected ***with traverse*** with the understanding that a divisional application can be filed to recapture product claims.

With regards to Applicants election the composition comprising the compound having the following structure



4-((2R, 5S)-4-[(R)-(4-Diethylcarbamoylphenyl)(3-hydroxyphenyl)methyl]-2,5-dimethyl-1-piperazinylmethyl) benzoic acid. Applicants respectfully remind the Examiner that when the generic claim is found patentable then all species claims should be examined and found patentable.

Rejection of claims 8, 14, 20-28 and 30-41 under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 8, 14, 20-28 and 31-40 under 35 U.S.C. §112, first paragraph because:

> "[T]he specification, while being enabling for treating the specific ischemic damage (*e.g.*, myocardial infarction) or reducing ischemic damage in cardiac tissue with the administration of 4-{(2R, 5S)-4-[(R)-(4-Diethylcarbamoylphenyl)(3-hydroxyphenyl)methyl]-2,5-dimethyl-1-piperazinylmethyl}benzoic acid, does not reasonably provide enablement for "reducing ischemic damage,"

> "protecting against ischemia and reperfusion injury," or "effectuating ischemic preconditioning of cardiac tissue" with the administration of [sic] compound of the formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims."

The Examiner concludes by stating

> As discussed above, although the specification describes working examples if using compound I having delta opioid receptor agonist for reducing ischemic damage to the heart tissue (intended treatment of myocardial infarction), there is no demonstrated correlation that the tests and results apply to the prevention or treatment of all of the disorders embraced by the instant claims. In view of the limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the predictability of the pharmaceutical art would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims."

Applicants respectfully traverse this rejection. However, to move prosecution forward, applicants have amended claim 14 to recite "A method of reducing ischemic damage *in cardiac tissue...*" and claim 31 has been amended to recite "A method of *treating* ischemia and reperfusion injury *in cardiac tissue...*", thus rendering the rejection moot as it pertains to the terms "reducing ischemic damage" and "protecting against ischemia and reperfusion injury," respectfully.

In regards to the term "effectuating ischemic preconditioning of cardiac tissue," Applicants argue that the specification is replete with examples and teachings of how the claimed compounds can be used for the "effectuation of ischemic preconditioning of cardiac tissue." The Merriam-Webster Dictionary defines the term "effectuation" or "effect" as "the power to bring about a result; influence" (see, *e.g.* "Effect." *Merriam-Webster Online Dictionary*. 2004. http:/www.merriam-webster.com (9 Jan. 2007)). The specification clearly teaches that the compounds of the present invention have the ability to bring about a result, or influence, ischemic preconditioning of cardiac tissue in a subject. For example, in Example 8 at page 34, line 10 through page 35, line 17, the specification teaches that pretreatment of cardiac tissue with the compound of the present invention prior to infarction (*i.e.* vessel occlusion) resulted in a dramatically reduced infarction size. Specifically, pretreatment of cardiac tissue with the compound of the present invention showed a 48% reduction in the infarct size relative to the control group, and after 7 days at the initial treatment, a 43% reduction was still exhibited in the infarct size relative to the non-treated control group (see page 35, lines 8-17).

Moreover, the specification further teaches in Example 9 that administration of the compound of the present invention prior to vessel occlusion "...produced ***clear protective effects*** in both studies tested up to doses of 1.0 mg/kg. Control groups indicated ischemic damage of ~50-55% of the area at risk (AAR). Compound I, administered at doses higher than 0.1 protected against between about 30 and 40% of this damage across both studies" (emphasis added) (see, *e.g.* page 37, lines 1-6 and Table 7). Lastly, Example 10 teaches that administration of the compound of the present invention after vessel occlusion, but prior to reperfusion (*i.e.* release of the occlusion) also resulted in ***clear protective effects***, with control cardiac tissue showing ~50% infarction damage at the area at risk as opposed to 30-40% infarction damage to treated cardiac tissue (see, *e.g.* page 37, lines 10-19). As can be clearly seen, the specification more than adequately teaches that the compound of the present invention effectuates the preconditioning of cardiac tissue.

Applicants further submit that the amendment of claim 31 renders moot the Examiners objection that "[t]here are no known compounds of similar structure have been demonstrated to prevent a disease of condition mediated by ischemic damage or ischemia and reperfusion injury." That said, Applicants wish to clarify for the Examiner the scope of the present invention. The purpose of the claimed compound of the present invention is ***not*** to cure diseases such as coronary artery disease, heart valve disease, arrhythmia, heart failure, stroke, shock, endocarditis, diseases or the aorta and its braches, disorders of the peripheral vascular systems, congenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiomyopathy, restinosis, ischemic disease, pulmonary edema associated with acute myocardial infarction, thrombosis, platelet aggregation, platelet adhesion, pulmonary thromboembolism, cerebral thromboembolism, arteriovenous fistula, and atheroembolism. Nor do Applicants claim that the single underlying mechanism that ties together all of these conditions is tissue damage caused by ischemia, as asserted by the Examiner (see Office Action at page 5, line 6 through page 6, line 15). Instead, what is within the scope of the present invention is that ischemic damage, such as those caused by a myocardial infarction, stroke, etc., is a common outcome associated with all of the above-mentioned conditions. The compounds of the present invention have been shown to help mitigate the amount of ischemic-related tissue damage in cardiac tissue after an ischemic incident (and subsequent reperfusion) as well as to produce a protective effect on cardiac tissue during subsequent ischemic incidents. As such, the administration of the compounds of the present invention ***will not cure*** the underlying disease or condition (*e.g.* coronary heart disease, pulmonary thromboembolism, platelet adhesion and the like) and as such is not a "magic bullet," but will likely increase the chance of survival of the patient should an ischemic incident occur by helping to reduce the amount of cardiac tissue damage at the time of the ischemic event or to precondition the patient's cardiac tissue so that when a subsequent ischemic event

occurs, the amount of tissue damage is significantly less. In view of the amendments to claims 8, 14 and 31 and the above discussion, Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of claim 8 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claim 8 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that: "Independent method claim 8 recites 'the composition according to claim 1.' Although the diarylmethylpiperazine compound of the formula (I) is recited in claim 1, it is considered that the meaning of the independent claim 8 should be clear from the wording of the claim alone."

Applicants have amended claim 8 to recite the specific structure of the diarylmethylpiperazine compound of the formula (I). As such, Applicants believe that this amendment makes clear the meaning of independent claim 8. Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of claims 8, 14, 20-23, 27-28, 33-34 and 38-40 under 35 U.S.C. §103(a)

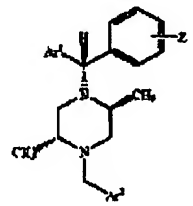
The Examiner has rejected claims 8, 14, 20-23, 27-28, 33-34 and 38-40 under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (U.S. 7,030,124 B2, hereinafter Chang '124) in view of Schultz *et al.* (US 6,103,722, hereinafter Schultz '722). According to the Examiner, "Chang teaches diarylpiperazine compounds of formula (I) including compounds (i), (vii), (viii), (xii), and (xiii) or pharmaceutically acceptable ester(s) ... for the treatment of depression" and Schultz teaches the "use of delta opioid receptor agonist including diarylmethylpiperazine compound such as BW373U86 and SNC80 as a cardioprotective agent for reducing ischemic damage or ischemia and reperfusion injury." Lastly, the Examiner states that "Chang differs from the claimed invention in (i) the selection of the specific species, namely 4-{(2R,5S)-4-[(R)-(4-diethylcarbamoylphenyl)(3-hydroxyphenyl)methyl]-2,5-dimethyl-1-piperazinylmethyl]benzoic acid and the administration of said compound to a patient having or at risk of having ischemia or ischemic event to reduce ischemic damage to the human heart." The Examiner concludes by stating "It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those of the claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties, thus, the same use as the genus as a whole."

Applicants vigorously disagree because the Chang '124 specification provides no teaching, suggestion or disclosure for the carboxy-substituted benzyl group at the "4" position. As described in the Chang '124

specification at column 2, line 18 through column 3, line 26, recreated below for ease of reference, there is no indication that a carboxyl-substituted benzyl group was even considered.

The present invention relates in one aspect to a method of combating a mood disorder in a subject experiencing or susceptible to same, comprising administering to said subject an effective amount of a therapeutic composition comprising a diarylmethylpiperazine compound of the general formula:

(I)



wherein:

Ar^1 is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1,

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl;

C_1–C_6 haloalkyl;

C_1–C_6 alkoxy;

C_3–C_6 cycloalkoxy;

sulfides of the formula SR^6 where R^6 is C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_3–C_6 cycloalkyl, aryalkyl having a C_7–C_{10} aryl moiety and a C_1–C_6 alkyl moiety, or C_6–C_{10} aryl;

sulfoxides of the formula SOR^6 where R^6 is the same as above;

sulfones of the formula SO_2R^6 where R^6 is the same as above;

nitrile;

C_1–C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCOOR^6$ where R^6 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_2–C_6 hydroxyalkyl, C_2–C_6 methoxyalkyl, C_3–C_6 cycloalkyl, or C_5–C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2–C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

R^4 is hydrogen, halogen, or C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl;

Z is selected from the group consisting of hydrogen, hydroxyl, halogen and alkoxy;

Ar^2 is a 5 or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a carbon atom thereof a substituent X

X is selected from the group consisting of hydrogen, halogen (fluorine, bromine, chlorine, iodine), hydroxy and alkoxy;

or a pharmaceutically acceptable ester or salt thereof.

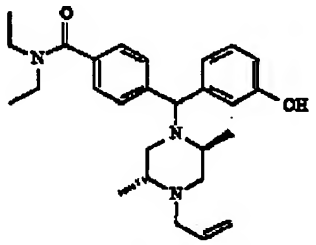
Instead, the substitution suggested by Chang '124 includes the following groups (from bracketed section above) and notably there is ***no disclosure or suggestion*** of the carboxy-substituted benzyl functional group.

> Ar^2 is a 5 or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a carbon atom thereof a substituent X
>
> X is selected from the group consisting of hydrogen, halogen (fluorine, bromine, chlorine, iodine), hydroxy and alkoxy;
>
> or a pharmaceutically acceptable ester or salt thereof.

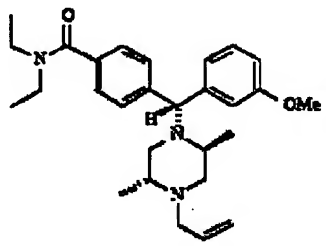
Applicants respectfully remind the Examiner that it is not proper to neither speculate on functional groups nor use impermissible hindsight. As such, the multiplicity of compounds in the Chang '124 reference does not render obvious Applicants' claimed compounds because the Chang '124 reference indicates a preference leading away from the claimed compounds, and most importantly, never discloses, teaches or suggests such a carboxy-substituted benzyl functional group.

Applicants further submit that the proposed combination of Chang '124 with Shultz '722 does not, in any way provide derivative basis for the invention of claims 8, 14, 20-23, 27-28, 33-34 and 38-40. As discussed above, the presently claimed compounds were not described, suggested, or taught in Chang '124 and the addition of Schultz '722 does not overcome the shortcomings of Chang '124.

Initially, it should be noted that the only diarylmethylpiperazines described in Schultz '722 include BW373U86 and SNC80 and having the structures below:



BW373U86 ((+/-)-3)



SNC80 ((+)-3)

Notably, these compounds ***do not*** have a carboxy-substituted benzyl ring at the "4" position of the piperazine group. In fact they do not even include a ring structure connected to the N of the piperazine group. Thus, this reference does not provide any additional disclosure over Chang '124.

Further, it is known that compounds such as BW373U86 and SNC80 have been implemented in causing seizures in dosed subjects due to their ability to pass between the blood/brain barrier (see, *e.g.*, the specification at page 3, line 25 through page 4, line 3). The compounds of the present invention, however, ***do not*** exhibit the potential of causing seizures in patients. As such, one skilled in the art ***would not*** be motivated to combine compounds such as BW373U86 as described in Schultz '722 with the compounds claimed in the present invention. Indeed, combining these compounds with those of the present invention would undermine one of the key benefits, namely, that the presently claimed compounds avoid the potential of seizures caused by administration of some mu and delta opioid receptor agonists. Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of claims 24-26, 31-32 and 35-37 under 35 U.S.C. §103(a)

The Examiner has rejected claims 24-26, 31-32 and 35-37 under 35 U.S.C. §103(a) as being unpatentable over Chang '124 in view of Schultz '722, and further in view of Applicant's admission of the prior art (page 9, lines 5-7), which states "[O]ther cardiac therapeutic agents may include, but are not limited to nitrates, beta-adrenergic blockers, calcium channel antagonists, ACE inhibitors, non-peptide angiotensin II antagonists, IIb/IIIa antagonists and aspirin." The Examiner also cites Oeltgen (U.S. 6,645,938, herein after Oeltgen '938) to demonstrate the state of the art knowledge in using arginine hydrochloride as a cardiac therapeutic agent. The Examiner asserts that:

> "[A]bove references in combination make clear that the diarylmethylpiperazine compound and the second agent (e.g., nitrates, beta-adrenergic blockers, calcium channel antagonist, ACE inhibitors, non-peptide angiotensin II antagonist, Ii [sic] b/IIIa antagonists and aspirin and arginine) have been individually used for the treatment of ischemia or ischemic damage to heart. It is obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination if active ingredient with the same character is merely the additive effect of each individual component. See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

Applicants respectfully traverse this rejection. Applicants have completely reviewed both references (Chang '124 and Schultz '722) and neither disclose, teach, or suggest Applicants' claimed compounds in combination with other cardiac therapeutic agents including nitrates, beta-adrenergic blockers, calcium channel antagonists, ACE inhibitors, non-peptide angiotensin II antagonists, IIb/IIIa antagonists and

RECEIVED
CENTRAL FAX CENTER
FEB 16 2007

aspirin. Thus, where is there any teaching or suggestion to go in the direction of Applicants? Clearly, there is none. The addition of Oeltgen '938 does not over come the shortcomings of Chang '124 and Schultz '722 because Oeltgen '938 merely teaches that an additional cardiac therapeutic agent, arginine hydrochloride, can be used in combination with a ***peptide*** molecule, not a diarylmethylpiperazine compound with a carboxylic acid in the "4" position.

Further in light of the fact that the claimed method recited in claim 20 is novel and inventive, the addition of an additional component does not alter the patentability of the original method. Thus, the inclusion of an additional therapeutic agent in a composition does not alter the fact that the claimed compounds of the present invention are novel and inventive over the art, as is the combination with another therapeutic compound.

In summary, Applicants request that all rejections to the pending claims be withdrawn in light of the amendments and arguments made above.

Fees Payable/Petition

Applicants request a one month extension in responding to the October 16, 2006 Office Action, thereby extending the date of response from January 16, 2007 to February 17, 2007. The petition fee is $60.00. The Commissioner is authorized to charge such fee and any addition fee found due for entry of this amendment to Deposit Account 13-4365 of Moore & Van Allen, PLLC.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Kwon reconsider the patentability of claims xxx in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Smith is requested to contact the undersigned attorney at (919) 286-8089 to resolve same.

Respectfully submitted,

Marianne Fuierer
Reg. No. 39,983
Attorney for Applicants

Attorney Docket No. 021353-118.130

Moore & Van Allen, PLLC
Telephone: (919) 286-8000
Facsimile: (919) 286-8199